CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74936

BIOEQUIVALENCE REVIEW(S)

ANDA 74-936

Purepac Pharmaceuticals Co.
Attention: Helena Goncalves
200 Elmore Avenue
Elizabeth NJ 07207

JAN 15 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Naproxen Delayed-release Tablets, 375 mg and 500 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 1000 mL of acid and buffer phases (USP<724> Method B) at 37°C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

   I. Not more than , (Q) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes under 0.1 N HCL acid phase.

   II. Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes under buffer phase, pH 6.8.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Naproxen-DR Tablets, USP
375 mg and 500 mg Tablets
ANDA #74-936
Reviewer:A.P.Patel
File:x\wpfile\biofinal\74936sdw.796

JAN 8 1997

Purepac, Co.
Elizabeth, NJ
Submission Date:
July 31, 1996

Review of Three Bioequivalence Studies and Dissolution Data

I. Objectives:

Review of Purepac's three *in vivo* bioequivalence studies comparing 375 mg and 500 mg strength Naproxen DR Tablets to Syntex's 375 mg and 500 mg strength, EC Naprosyn® Tablets under fasting and non-fasting conditions. The firm has also submitted *in vitro* dissolution data for review.

Introduction:

Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Naproxen is indicated for the treatment of ankolysing spondylitis, juvenile arthritis, osteoarthritis and rheumatoid arthritis. The Naproxen delayed-release tablets dissolves above pH 6. In fasted subjects, peak plasma levels following first dose are reached in 4-5 hours(range 2 - 12 hours). In non-fasted subjects , peak plasma levels are reached in about 12 hours (range 4-24 hours). The absorption the drug has been shown to be delayed until the stomach is emptied. The elimination half-life of naproxen is 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days.

II. Summary of Bioequivalence Study Procedures:

A. BE Study under Fasting Conditions for 375 mg tablets:

1. Protocol and Study# 952276

2. **Objective and Study Design:**

A randomized, single-dose, two-period, two-treatment, two-sequence crossover study (two week wash-out period) was conducted assessing the relative bioavailability of Purepac's Naproxen DR 375 mg (Batch#PI-917) tablets *vs* Syntex's EC-Naprosyn ® 375 mg tablets (Lot# 04480) under fasting condition.

3. **Study sites:**

Clinical Facility: **Analytical Facility:**

Institutional Review Board Approval: Protocol approved by IRB

5. **Study dates:**

Period 1	April 23, 1996
Period 2	May 7, 1996

6. **Drug Products:**
A. Test: 375 mg Naproxen DR Tablets (Purepac, Lot #PI-917, Exp. 2/98, batch size yield 86.6%). Mean uniformity 99.3% cv 1.2% (n=10).
B. Reference: 375 mg EC-Naprosyn® Tablets (Syntex, Lot #04480, Exp. 1/98, batch size - N/A). Mean uniformity 98.6% cv 1.2% (n=10).
All doses were administered with 240 ml of ambient temperature water following an overnight (10 hour) fast.

7. **Subjects:**Twenty-six subjects who entered in this study were normal healthy male volunteers with a mean age of 27.9 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. **Confinement:** During the confinement periods of this study, the subjects were housed and fed at the clinical facility.

9. **Food and fluid intake:** Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of tap water. Water intake was restricted from 1 hour before until 2 hours after dose and there after was allowed ad lib.

10. **Washout period:** 14 days between periods

11. **Blood samples:** In each period, 5 mL of blood samples were collected in EDTA containing purple-top tubes at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours. Plasma was separated and stored frozen at -20°C or below until analyzed.

12. **Subject safety monitoring:** Subjects were monitored for vital signs and were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. **Adverse events:** At each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. **Analytical procedure**

15. **Pharmacokinetics and statistical analysis:** Statistical analyses were performed on the pharmacokinetics parameters for Naproxen DR. The 90% confidence intervals were calculated for log-transformed AUCt, AUCi and Cmax PK parameters as per FDA requirements.

B. BE Study under Fasting Conditions for 500 mg tablets:

1. Protocol and Study# 960458

2. **Objective and Study Design:**

A randomized, single-dose, two-period, two-treatment, two-sequence crossover study (two week wash-out period) was conducted assessing the relative bioavailability of Purepac's Naproxen DR 500 mg (Batch#PI-919) tablets *vs* Syntex's EC-Naprosyn ® 500 mg tablets (Lot# B0205) under fasting condition.

3. **Study dates:**

	Period 1	March 26, 1996
	Period 2	April 9, 1996

4. **Drug Products:**

A. Test: 500 mg Naproxen DR Tablets (Purepac, Lot #PI-919, Exp. 2/98, batch size yield 89.6%). Mean uniformity 98.1% cv 0.9% (n=10).

B. Reference: 500 mg EC-Naprosyn® Tablets (Syntex, Lot #B0205, Exp. 4/98, batch size - N/A). Mean uniformity 98.7% cv 1.1% (n=10).

All doses were administered with 240 ml of ambient temperature water following an overnight (10 hour) fast.

5. **Subjects:**Twenty-six subjects who entered in this study were normal healthy male volunteers with a mean age of 25.6 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

6. Details of other categories described above under 375 mg fasting study is also applicable to the 500 mg fasting study.

C. BE Study under non-fasting Conditions:

1. Protocol and Study # 952275

2. **Objective of the study:**

The objective of this study was to determine the bioequivalence of two Naproxen DR formulations after administration of single doses to healthy volunteers under non-fasted conditions.

3. **Study sites: As described under fasting study**

Institutional Review Board Approval: Protocol approved by IRB

4. **Study dates:**

Period 1	April 1, 1996
Period 2	April 15, 1996
Period 3	April 29, 1996

5. **Drug Products:**

A. Test: 500 mg Naproxen DR Tablets (Purepac, Lot #PI-919, Exp. 2/98, batch size yield 89.6%)

B. Test: 500 mg Naproxen DR Tablets (Purepac, Lot #PI-919, Exp. 2/98, batch size eld 89.6%) dosed following high-fat breakfast.

C. Reference: 500 mg EC-Naprosyn® Tablets (Syntex, Lot #B0205, Exp. 4/98, batch size - N/A) dosed following high-fat breakfast. All doses were administered following over-night fast with 240 ml of room temperature water.

6. **Subjects:**Seventeen subjects entered the clinical study were normal healthy male volunteers with a mean age of 25.8 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations showing absence of any clinically significant findings. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

7. Details of other categories described above under 375 mg fasting study is also applicable to the 500 mg non-fasting study.

III. **Validation of Assay Method for Plasma Samples:**

IV. *In Vivo* BE Study Results with Statistical Analysis:

A. Study under fasting conditions:

A total of 26 subjects participated in the study and 24 subjects completed two periods of clinical study successfully. Two subjects dropped out (#18 and #23) for reasons not related to the study and their data were not included in the analysis.

Adverse events: No clinically significant adverse events were reported.

1. Mean plasma levels

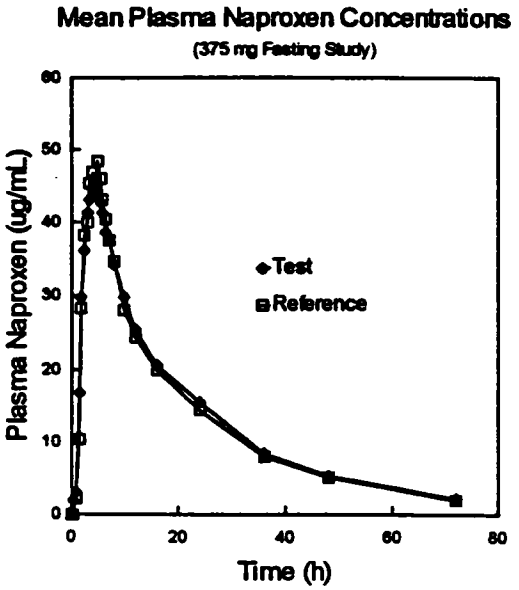
The mean plasma levels for the test and reference products are comparable as shown in Table 1. The test/reference (T/R) ratios for the mean plasma levels ranged from 0.90 to 1.60, between 1 hour and 72 hours post-dose. The T/R ratio was greater than 1.0 between predose (0 hours) and 0.5 hours post-dose due to interference at naproxen retention time for subject #9.

Table 1. Mean plasma concentrations of test and reference naproxen, 375 mg study. The presence of mean plasma naproxen concentration at time zero is due to subject #9 at both dosing periods. It was reported that subject #9 had entity in his plasma which interfered with the naproxen retention time. The firm has evaluated the study data with and without subject #9 and show that the outcome of the study was not affected (see appendix S- 4, orange volume 1 of 7, pages 418 - 422).

Table 1. Mean Plasma Naproxen Levels for 375 mg Fasting Study.

Mean Plasma Levels of Naproxen (ug/mL)

Time	Test		Reference		Ratio
(h)	Mean	% CV	Mean	% CV	(T/R)
0.0	0.53	489.90	0.03	489.90	15.81
0.5	2.05	348.34	0.04	489.90	50.63
1.0	3.17	267.55	2.32	309.17	1.37
1.5	16.78	163.50	10.47	181.20	1.60
2.0	29.89	102.68	28.23	99.67	1.06
2.5	36.15	80.75	38.18	75.95	0.95
3.0	41.29	64.87	40.00	60.48	1.03
3.5	43.13	54.48	45.40	47.02	0.95
4.0	44.60	45.46	46.83	42.02	0.95
4.5	46.08	43.57	45.47	39.03	1.01
5.0	43.70	37.67	48.33	20.36	0.90
5.5	42.76	28.08	45.87	22.38	0.93
6.0	41.35	25.44	43.08	24.19	0.96
6.5	38.63	23.87	40.38	25.99	0.96
7.0	37.63	23.21	37.51	20.44	1.00
8.0	34.20	21.80	34.73	20.85	0.98
10.0	29.83	22.13	28.12	21.53	1.06
12.0	25.50	21.88	24.33	21.57	1.05
16.0	20.65	22.10	19.98	21.94	1.03
24.0	15.51	24.40	14.32	22.18	1.08
36.0	8.46	32.74	8.01	30.14	1.06
48.0	5.37	39.15	5.08	34.99	1.06
72.0	2.26	50.84	2.03	40.04	1.12



2. **Summary of Pharmacokinetic Data:** Table 2 and 3. Describes Mean plasma naproxen pharmacokinetic and 90% C.I. data for 375 mg fasting study (please see attachment for individual PK data, #101 - 02).

Table 2. Mean PK parameters:

Parameter	Test Mean (%CV)	Reference Mean (%CV)	Ratio (T/R)
AUC_{0-t} (ug/mL x h)	935.4 (23.6)	904.2 (18.8)	1.03
AUC_{0-inf} (ug/mL x h)	994.5 (26.0)	955.3 (20.1)	1.04
C_{max} (ug/mL)	61.14 (25.2)	63.6 (19.8)	0.96
Tmax (h)	4.07 (59.1)	3.44 (34.9)	1.18
Kelm (h^{-1})	0.0415 (14.3)	0.0421 (13.5)	0.99
T-half (h)	17.04 (14.3)	16.75 (12.9)	1.02

Table 3. Ln-transformed PK parameters:

Parameter	Test LS Means (%CV)	(Reference) LS Means (%CV)	Ratio (T/R)	90% C. I.
ln AUC_{0-t}	6.82 (3.01)	6.79 (2.53)	1.00	99.7 - 105.9
ln AUC_{0-inf}	6.88 (3.22)	6.85 (2.67)	1.00	99.9 - 106.6
ln C_{max}	4.08 (6.26)	4.13 (4.73)	0.99	88.3 - 102.1

The 90% C.I. are within the Agency's bioequivalence requirements, between 80% - 125%, fasting study is acceptable. The ratio of test/reference for pharmacokinetic parameters are not different from each other.

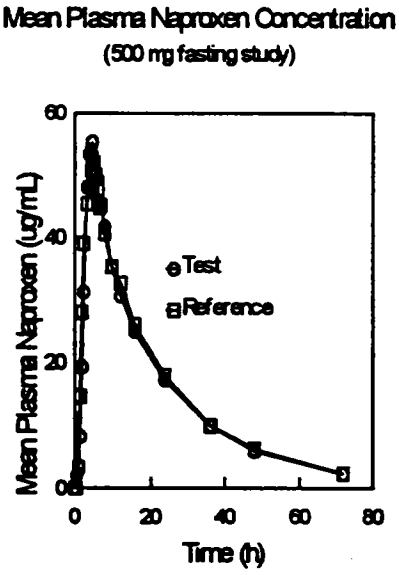
B. **Study under fasting conditions:** 500 mg Naproxen - DR
A total of 24 (and 2 alternate) male subjects participated in the study and 23 subjects completed two periods of clinical study successfully. One subject dropped out (#13) for reasons not related to the study and his data was not included in the analysis.

Adverse events: No clinically significant adverse events were reported.

1. **Mean plasma levels**
The mean plasma levels for the test and reference products are comparable as shown in Table 4. The test/reference (T/R) ratios for the mean plasma levels ranged from 0.58 to 1.11.

Table 4. Mean Plasma Naproxen levels for 500 mg Fasting Study

	Mean Plasma Naproxen (ug/mL)				
Time	Test		Reference		Ratio
(h)	Mean	%CV	Mean	%CV	(T/R)
0.0	0.00	0	0.00	0.00	0.00
0.5	2.00	381.23	0.00	0.00	0.00
1.0	3.74	371.11	3.58	310.71	1.04
1.5	8.56	193.41	14.79	153.87	0.58
2.0	19.37	151.97	27.94	105.61	0.69
2.5	31.40	84.18	39.11	74.54	0.80
3.0	47.92	58.9	45.40	61.51	1.06
3.5	53.43	48.37	48.17	47.14	1.11
4.0	54.00	41.91	50.57	45.00	1.07
4.5	55.22	38.47	52.55	30.79	1.05
5.0	51.19	34.57	52.09	27.13	0.98
5.5	50.36	26.94	50.16	30.46	1.00
6.0	49.50	24.87	47.80	28.88	1.04
6.5	45.86	25.46	44.70	29.66	1.03
7.0	45.11	25.33	45.15	31.85	1.00
8.0	41.62	22.73	40.64	29.50	1.02
10.0	35.23	21.66	35.24	21.08	1.00
12.0	30.69	23.49	32.89	36.90	0.93
16.0	25.15	27.41	26.04	35.19	0.97
24.0	17.53	34.62	18.17	32.13	0.96
36.0	10.04	36.45	10.04	33.56	1.00
48.0	6.19	39.02	6.30	36.52	0.98
72.0	2.39	42.19	2.46	47.80	0.97



2. **Summary of Pharmacokinetics Data:** Table 5 and 6. Describes the Mean plasma naproxen pharmacokinetics data and 90% C.I. for 500 mg fasting study (please see attachment for individual PK data, # 1306 - 07).

Table 5. Mean PK parameters (non transformed):

Parameter	Test Mean (%CV)	Reference Mean (%CV)	Ratio (T/R)
AUC_{0-t} (ug/mL x h)	1082.67 (20.11)	1105.75 (21.00)	0.98
AUC_{0-inf} (ug/mL x h)	1140.79 (21.32)	1166.13 (22.46)	0.98
C_{max} (ug/mL)	71.61 (23.11)	68.88 (16.14)	1.04
Tmax (h)	4.19 (68.44)	4.21 (52.54)	1.00
Kelm (h^{-1})	0.043 (12.05)	0.044 (13.03)	0.98
T-half (h)	16.27 (12.01)	16.18 (13.48)	1.01

Table 6. Ln-transformed PK parameters and 90% C.I.:

Parameter	Test LS Means (%CV)	(Reference) LS Means (%CV)	Ratio (T/R)	90% C. I.
ln AUC_{0-t}	6.67 (2.89)	6.99 (2.96)	0.95	94.9 - 101.3
ln AUC_{0-inf}	7.02 (3.04)	7.04 (3.12)	1.00	94.8 - 101.4
ln C_{max}	4.24 (5.89)	4.22 (4.17)	1.00	91.8 - 114.5

The 90% C.I. are within the Agency's bioequivalence requirements, between 80% - 125%, fasting study is acceptable. The ratios of test/reference for pharmacokinetic parameters are not different from each other.

C. **Study under non-fasting conditions:** For 500 mg Naproxen - DR.
A total of 17 male subjects participated and completed clinical study successfully.

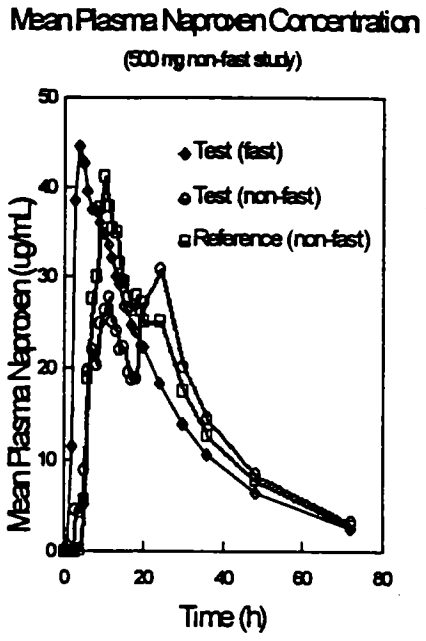
Adverse events: No clinically significant adverse events were reported.

1. **Mean plasma levels**

The mean plasma levels for the test and reference products are comparable as shown in Table 7. The non fasted test/reference (T/R) ratios for the mean plasma levels ranged from 0.64 to 1.58 with 15.61 at 4 hour post-dose. The plasma naproxen profiles for test (non-fast) and reference (non-fast) shows some differences (Table 7).

Table 5. Mean Plasma Naproxen levels for 500 mg non fasting study.

Mean Plasma Naproxen Concentrations (ug/mL)							
Time	Test fast		Test non-fast		Reference non-fast		Ratio non-fast
(h)	Mean	%CV	Mean	%CV	Mean	%CV	(T/R)
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	0.79	412.31	0.00	0.00	0.00	0.00	0.00
2.0	11.41	167.92	0.00	0.00	0.00	0.00	0.00
3.0	38.50	74.10	4.48	412.31	0.00	0.00	0.00
4.0	44.51	59.04	4.37	412.31	0.28	412.31	15.61
5.0	42.67	45.74	8.94	217.46	5.67	290.01	1.58
6.0	39.59	39.31	19.72	140.72	18.91	150.72	1.04
7.0	37.45	38.10	21.88	117.56	27.60	102.26	0.79
8.0	37.40	27.91	20.28	115.54	30.11	88.44	0.67
9.0	36.18	30.62	24.96	92.27	37.81	67.62	0.66
10.0	34.93	23.98	26.26	88.08	41.29	52.53	0.64
11.0	33.59	23.31	27.78	82.19	37.90	52.49	0.73
12.0	32.20	20.05	25.06	82.72	35.35	40.76	0.71
13.0	30.02	16.80	24.04	80.12	35.02	45.81	0.69
14.0	29.32	22.79	21.91	79.36	31.54	42.39	0.69
15.0	26.71	20.09	22.09	83.86	29.53	41.42	0.75
16.0	26.34	25.00	19.56	78.88	27.72	41.57	0.71
17.0	24.74	22.32	18.56	77.73	26.28	36.85	0.71
18.0	23.82	25.76	18.79	68.09	28.03	44.57	0.67
19.0	22.38	24.68	26.06	69.73	26.38	42.38	0.99
20.0	22.10	26.21	27.23	75.30	25.15	41.32	1.08
24.0	18.27	25.38	30.92	52.45	25.11	39.76	1.23
30.0	13.97	25.81	20.21	36.75	17.42	40.75	1.16
36.0	10.61	26.58	14.57	33.80	12.62	36.82	1.15
48.0	6.46	27.54	8.51	36.92	7.91	38.22	1.08
72.0	2.59	26.99	3.26	35.70	2.98	40.64	1.10



2. **Summary of Pharmacokinetics Data:** Table 8 and 9. Describes the mean plasma naproxen pharmacokinetic data for 500 mg non-fasted study (please see attachment for individual PK data, # 2407 - 76).

Table 8. Untransformed PK parameters (non-fasted study):

Parameter	Test- Fast Mean (%CV)	Test Mean (%CV)	Reference Mean (%CV)	Ratio (T/R)
AUC_{0-t} (ug/mL x h)	1048.7 (11.0)	1105.75 (21.00)	1034.1 (15.5)	1.07
AUC_{0-inf} (ug/mL x h)	1114.0 (11.9)	1166.13 (22.46)	1107.3 (15.6)	1.05
C_{max} (ug/mL)	59.46 (24.8)	68.88 (16.14)	63.10 (15.5)	1.09
Tmax (h)	5.59 (69.0)	*14.30 (52.3)	*10.06 (46.7)	1.42
Kelm (h^{-1})	0.041 (11.4)	0.044 (13.03)	0.041 (9.7)	1.07
T-half (h)	17.12 (12.0)	16.02 (11.4)	16.7 (9.7)	0.96

*Test tmax lag 4.24 hours and Reference tmax lag 2.41 hours.

Table 9. *Ln-transformed PK parameters :

Parameter	Test (Fast) Means (%CV)	Test Means (%CV)	Reference Means (%CV)	Ratio (T/R)
ln AUC_{0-t}	1042.90 (10.8)	998.67 (13.2)	1023.04 (15.0)	0.98
ln AUC_{0-inf}	1106.83 (11.7)	1074.19 (13.8)	1095.0 (15.4)	0.98
ln C_{max}	57.73 (25.6)	57.49 (27.1)	62.35 (16.3)	0.92

* antilog of geometric means

The test/reference ratios for pharmacokinetic parameters under non-fasted conditions are close to unity and satisfy FDA requirements.

The time to peak naproxen plasma level of test and reference tablet is different. The mean test (non-fast) plasma naproxen data indicates two major peaks at 11 hours and 24 hours. The reference data indicates a single major peak at 10 hours and a small shoulder peak at 18 hours. The plasma naproxen levels, Cmax, Tmax, and Tmax adjusted (Tmax - lag time) under non-fasted conditions were evaluated by non-parametric t-test statistics. The median values of each parameter was not statistically significant at $p < 0.05$ level. The test and reference AUC under non-fasted condition is not different. PDR (1996) monograph for EC-Naprosyn indicates time to peak plasma level varies between 4 - 24 hours with food, without affecting peak naproxen levels (Cmax). The test (non-fasted) Tmax range is 3 - 24 hours and reference Tmax range is 5 - 24 hours. The absorption of drug from enteric coated dosage form is greatly limited by gastric emptying.

D. Waiver of in vivo non-fasted biostudy for 375 mg tablet:

The firm has conducted an acceptable fasting study, dissolution test and the 375 mg formulation is proportionally similar to 500 mg tablet which has met acceptable biostudy requirements. A waiver of in vivo non-fasted biostudy can be granted.

E. Formulations:

Table 10. Shows comparative formulation of 375 mg and 500 mg Naproxen -DR tablets.

COMPONENTS	Amount (mg)/Tablet		Ratio
Tablet Core:	**375 mg**	**500 mg**	**(500/375)**
Naproxen	375	500	1.33
Croscarmellose Sodium NF			
Povidone USP			
Purified Water USP			
Magnesium Stearate NF			
Total Core Weight:			
Enteric Coat:			
Purified Water USP			
Sodium Hydroxide			
Chroma-Teric Yellow			
Printing Ink. Black,			
Total Tablet Weight:	**462**	**616 mg**	1.33

The components in 375 mg and 500 mg tablets are proportional.

F. In-Vitro Dissolution Test:

The firm has used USP23 <724> Method B For delayed release (DR) or enteric coated (EC) formulation. The test has an acid phase (0.1 N HCL acid) and a sodium phosphate buffer phase (pH 6.8) dissolution time profile, data are shown in Table 9.

In addition, the firm has demonstrated that in the acid stage there was tablet integrity and negligible dissolved drug below pH 6.8. On one occasion, out of four separate in vitro acid phase studies, 9.2% of the drug was dissolved in the acid stage (below USP's dissolved drug in acid stage). The firm has tabulated observation of tablet integrity under the various acid/buffer combinations.

Table 11. In Vitro Dissolution Testing: USP 23 <724> Method B, p1796.
Drug: Naproxen - DR
Dose Strength: 375 mg and 500 mg tablets
ANDA No.: 74-723
Firm: Purepac Pharmaceutical Co.

I. Conditions for Dissolution Testing (USP Dissolution Method):

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Mediums: 0.1N HCL for 120' followed by Sodium phosphate buffer, pH 6.8 for 60'.
Volume: 1000 mL acidic and buffer stages at 37°C.
Sampling Times:
acidic stage: 60 and 120 minutes
buffer stage: 10, 20, 30, 45, and 60 minutes.
Specifications: NMT (Q) / 120 min. (acidic stage)
NLT (Q) / 45 min. (buffer stage)
Assay Methodology:
Reference Drug: EC-Naprosyn 375 and 500 mg DR tablets (Syntex)
Time: Acidic stage 120 min; Buffer stage 60 min; Total run time 180 min.

II. Results of In Vitro Dissolution Testing: 375 mg tablets

Time (minutes) Stage I (acid)	Test 375 mg tablet Batch# PI-917 (n=12) MEAN	RANGE	%CV	Reference 375 mg tablets Batch# 04480 (n=12) MEAN	RANGE	%CV
60	0.0		346.4	0.1		86.1
120	0.0		233.5	0.1		42.6
Stage II (buffer)						
10	0.6		20.6	1.1		66.3
20	35.2		54.0	42.8		23.4
30	86.8		4.9	87.8		8.3
45	**94.4**		**1.7**	**99.8**		**1.5**
60	96.7		1.5	100.8		0.8

III. Results of In Vitro Dissolution Testing: 500 mg tablets

Time (minutes) Stage I (acid)	Test 500 mg tablet Batch# PI-919 (n=12) MEAN	RANGE	%CV	Reference 500 mg tablets Batch# B0205 (n=12) MEAN	RANGE	%CV
60	0.0		-	0.0		-
120	0.0		-	0.0		-
Stage II (buffer)						
10	0.7		7.4	0.4		14.6
20	44.1		45.1	16.9		53.6
30	87.8		5.6	81.7		13.2
45	**96.0**		**1.6**	**99.0**		**2.8**
60	98.6		1.1	101.0		1.1

The firm has conducted the required comparative dissolution tests on 375 mg and 500 mg tablets from the bio-batch. The comparative (test vs reference) dissolution test is acceptable.

V. Comments

1. **Study of 375 mg and 500 mg tablets under fasting conditions:**

   375 mg Naproxen - DR:

   Twenty-six subjects participated in the study and 24 subjects completed two periods of clinical study successfully. Two subjects dropped out (#18 and #23) for reasons not related to the study and their data were not included in the analysis. The mean plasma levels for the test and reference products are comparable. The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and Cmax were within the 80-125% range.

   500 mg Naproxen - DR:

   Twenty-four male subjects participated in the study and 23 subjects completed two periods of clinical study successfully. Subject #13 dropped out for reasons not related to the study and his data was not included in the analysis. The mean plasma levels for the test and reference products are comparable. The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and Cmax were within the 80-125% range.

2. **Study of 500 mg Naproxen - DR tablet under non-fasting Conditions:**

   Seventeen subjects were enrolled and all completed three periods of the study successfully. There was no missing sample. With food, the time to peak of test and reference tablet was different. The test (non-fasted) Tmax ranged 3 - 24 hours and reference Tmax ranged 5 - 24 hours. The plasma naproxen, Cmax, Tmax, and Tmax adjusted (Tmax - lag time) under non-fasted conditions were evaluated by non-parametric statistics. The median values of each parameter was not statistically significant at $p < 0.05$ level. The test and reference AUC under non-fasted condition was not different. The PDR (1996) monograph for EC-Naprosyn indicates time to peak plasma level varies between 4 - 24 hours with food. Absorption of the drug from enteric coated dosage forms is greatly limited by gastric emptying. The test/reference ratios for ln-transformed AUCt, AUCi and Cmax are near unity and meet the Agency's requirements.

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   It is note worthy to point out that the difference in the PK parameters (AUCt, AUCi and Cmax) for 375 mg and 500 mg fasting study data are not dose proportional. This is in agreement with Niazi et al. (Biopharm. Drug Dispos. 17:355-61, 1996).

3. **Waiver of in vivo non-fasted bio-study for 375 mg tablet:**

   Waiver from *in vivo* bioequivalence requirements is approveable. The dissolution test conducted by Purepac, on its Naproxen 375 mg tablets (Batch# PI-917), is acceptable. The formulation for the 375 mg strength is proportionally similar to the 500 mg strength of the test product which underwent acceptable bioequivalence testing.

Validation of assays and stability data are acceptable.

5. **Adverse events:**
   No clinically significant adverse events requiring medical attention were reported under the fasting and non-fasted studies.

6. The batch size of the 375 mg and 500 mg test product was and .ablets, respectively.

7. The formulation of the 375 mg and 500 mg test products are proportional in active and inactive ingredients.

8. **Dissolution testing:**
   The firm has used USP23 <724> Method B for delayed release (DR) or enteric coated (EC) formulation. The test has an acid (0.1 N HCL acid) stage and a sodium phosphate buffer (pH 6.8) stage dissolution time profile. Dissolution data are acceptable and tolerance "Q" is NLT dissolved in 45 minutes.

VI. **Deficiency:** None

VII. **Recommendation**

1. The single-dose bioequivalence study #952276 conducted under fasting conditions by Purepac Pharmaceuticals, on its Naproxen 375 mg Tablets (Batch# PI-917) comparing it to EC-Naprosyn^R 375 mg Tablets (Batch# 04480) manufactured by Syntex, is found to be acceptable by the Division of Bioequivalence. The study demonstrates that Purepac's Naproxen Tablet, 375 mg is deemed bioequivalent to the reference product, EC-Naprosyn^R Tablets, 375 mg, manufactured by Syntex.

2. The single-dose bioequivalence studies #960458 conducted under fasting conditions and #952275 conducted under non fasting conditions by Purepac Pharmaceuticals, on its Naproxen 500 mg Tablets (Batch# PI-919) comparing it to EC-Naprosyn^R 500 mg Tablets (Batch# B0205) manufactured by Syntex, are found to be acceptable by the Division of Bioequivalence. The studies demonstrate that Purepac's Naproxen 500 mg Tablet, is deemed bioequivalent to the reference product EC-Naprosyn^R 500 mg Tablet, manufactured by Syntex.

3. The dissolution testing conducted by Purepac Pharmaceuticals, on its Naproxen 375 mg tablets (Batch# PI-917) and 500 mg tablets (Batch# PI-919), is acceptable. The formulation for the 375 mg strength is proportionally similar to the 500 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* non-fasted bioequivalence study requirements for the test 375 mg tablet is granted. The Division of Bioequivalence deems Naproxen Tablet, 375 mg, manufactured by Purepac

Pharmaceuticals to be bioequivalent to EC-Naprosyn[R] Tablet, 375 mg, manufactured by Syntex.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of acid and buffer phases (USP<724> Method B) at 37°C using USP 23 apparatus 2 (paddle) at 50 RPM. The test drug should meet the following specifications:

   I. Not more than of the labeled amount of the drug in the dosage form is dissolved in 120 minutes under 0.1 N HCL acid phase.

   II. Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes under buffer phase, pH 6.8.

5. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approved.

   The firm should be informed of the recommendations.

1/8/97

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE Date: 1/8/97
Ramakant M. Mhatre, Ph.D.
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Concur
Rabindra Patnaik, Ph.D. Date: 1/8/97
Acting Director
Division of Bioequivalence

cc: ANDA# 74-936 (orignal, duplicate), A.P.Patel, Drug file, Division file

Table D3
Project Number :952276 375 mg fasting study
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac (A)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1									
2	2									
3	1									
4	2									
5	2									
6	1									
7	2									
8	1									
9	2									
10	1									
11	2									
12	1									
13	2									
14	1									
15	1									
16	1									
17	2									
19	2									
20	1									
21	1									
22	2									
24	2									
25	1									
26	2									
Arithmetic Mean		935.4	994.5	94.46	61.144	4.065	0.04147	17.04		
± SD		220.81	258.59	2.107	15.3810	2.4038	0.005925	2.429		
CV%		23.6	26.0	2.2	25.2	59.1	14.3	14.3		
n		24	24	24	24	24	24	24		

Attachments

Table D4
Project Number :952276 375 mg fasting
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Syntex (B)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	2									
2	1									
3	2									
4	1									
5	1									
6	2									
7	1									
8	2									
9	1									
10	2									
11	1									
12	2									
13	1									
14	2									
15	2									
16	2									
17	1									
19	1									
20	2									
21	2									
22	1									
24	1									
25	2									
26	1									
Arithmetic Mean		904.2	955.3	94.87	63.602	3.438	0.04208	16.75		
± SD		170.08	192.23	1.763	12.6072	1.2007	0.005691	2.155		
CV%		18.8	20.1	1.9	19.8	34.9	13.5	12.9		
n		24	24	24	24	24	24	24		

22-05-1996

Table D3
Project Number :960458 500 mg fasting
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac (A)

11:20

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1									
2	1									
3	1									
4	2									
5	2									
6	2									
7	1									
8	1									
9	2									
10	1									
11	2									
12	1									
14	1									
15	2									
16	1									
17	2									
18	1									
19	2									
20	1									
21	1									
22	2									
23	2									
24	2									
26	2									
Arithmetic Mean		1082.8	1140.8	95.14	71.606	4.188	0.04317	16.28		
± SD		217.85	243.24	1.690	16.5492	2.8659	0.005186	1.948		
CV%		20.1	21.3	1.8	23.1	68.4	12.0	12.0		
n		24	24	24	24	24	24	24		

22-05-1996

Table D4
Project Number :960458
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Syntex (B)

500 mg fasting

11:20

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	2									
2	2									
3	2									
4	1									
5	1									
6	1									
7	2									
8	2									
9	1									
10	2									
11	1									
12	2									
14	2									
15	1									
16	2									
17	1									
18	2									
19	1									
20	2									
21	2									
22	1									
23	1									
24	1									
26	1									
Arithmetic Mean		1105.8	1166.0	95.12	68.879	4.208	0.04356	16.18		
± SD		232.28	261.91	1.989	11.1198	2.2112	0.005674	2.182		
CV%		21.0	22.5	2.1	16.1	52.5	13.0	13.5		
n		24	24	24	24	24	24	24		

28-06-1996 10:21

Table D4
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac fasted (A)

Sorry non-fasting study. Test fasted.

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	tmaxadj (h)	Tlag (h)
1	2							
2	3							
3	1							
4	1							
5	3							
6	2							
7	2							
8	3							
9	1							
10	3							
11	3							
12	2							
13	2							
14	3							
15	1							
16	1							
17	1							
Arithmetic Mean		1048.7	1114.0	94.24	59.457	5.589	3.942	1.647
± SD		115.72	132.26	1.644	14.7491	3.8573	3.5256	0.8618
CV%		11.0	11.9	1.7	24.8	69.0	89.4	52.3
n		17	17	17	17	17	17	17

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Table D5
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac fasted (A)

Subject ID	Period	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	2				
2	3				
3	1				
4	1				
5	3				
6	2				
7	2				
8	3				
9	1				
10	3				
11	3				
12	2				
13	2				
14	3				
15	1				
16	1				
17	1				
Arithmetic Mean		0.04100	17.12		
± SD		0.004672	2.052		
CV%		11.4	12.0		
n		17	17		

28-06-1996

Table D6
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac fed (B)

Test fed

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	tmaxadj (h)	Tlag (h)
1	3							
2	1							
3	3							
4	2							
5	1							
6	3							
7	1							
8	1							
9	2							
10	2							
11	2							
12	3							
13	1							
14	2							
15	2							
16	3							
17	3							
Arithmetic Mean		1007.1	1084.1	93.01	59.256	14.298	4.239	10.059
± SD		137.99	155.76	2.723	13.7837	7.4840	4.5732	6.9144
CV%		13.7	14.4	2.9	23.3	52.3	107.9	68.7
n		17	17	17	17	17	17	17

Table D7
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Purepac fed (B)

Subject ID	Period	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	3				
2	1				
3	3				
4	2				
5	1				
6	3				
7	1				
8	1				
9	2				
10	2				
11	2				
12	3				
13	1				
14	2				
15	2				
16	3				
17	3				
Arithmetic Mean		0.04380	16.02		
± SD		0.004890	1.822		
CV%		11.2	11.4		
n		17	17		

Table D8
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation Ref. Fed.
Formulation: Syntex fed (C)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	tmaxadj (h)	Tlag (h)
1	1							
2	2							
3	2							
4	3							
5	2							
6	1							
7	3							
8	2							
9	3							
10	1							
11	1							
12	1							
13	3							
14	1							
15	3							
16	2							
17	2							
Arithmetic Mean		1034.1	1107.3	93.46	63.101	10.060	2.413	7.648
± SD		160.02	173.18	2.361	9.7531	4.6962	0.9389	4.4567
CV%		15.5	15.6	2.5	15.5	46.7	38.9	58.3
n		17	17	17	17	17	17	17

Table D9
Project Number :952275
Naproxen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Syntex fed (C)

Subject ID	Period	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1				
2	2				
3	2				
4	3				
5	2				
6	1				
7	3				
8	2				
9	3				
10	1				
11	1				
12	1				
13	3				
14	1				
15	3				
16	2				
17	2				
Arithmetic Mean		0.04149	16.85		
± SD		0.004010	1.632		
CV%		9.7	9.7		
n		17	17		

Table D10
Project Number :952275
Naproxen in Plasma
Ratio Analysis - AUC 0-t (mcg·h/mL)

Subject	(A)	(B)	(C)	(B/A)%	(B/C)%
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
Arithmetic Mean	1048.7	1007.1	1034.1	95.97	98.01
± SD	115.72	137.99	160.02	6.549	8.945
CV%	11.0	13.7	15.5	6.8	9.1
n	17	17	17	17	17

Purepac fed (B) vs Purepac fasted (A)
Purepac fed (B) vs Syntex fed (C)